that could oxidize polycyclic aromatic hydrocarbons ("PAHs") such as phenanthrene, fluoranthene, and pyrene. In addition, the Schmid group recently reported mutants of P450 BM-3 that can hydroxylate a variety of nonnatural substrates, including octane, several aromatic compounds and heterocyclic compounds (Appel et al., 2001). In addition, P450 BM-3 mutants for epoxidation of substrates such as long-chain unsaturated fatty acids (Miura and Fulco, 1975; Capdevila et al., 1996; Graham-Lorence et al., 1997; Ruettinger and Fulco, 1981) and styrene (Fruetel, J A et al., 1994) have been suggested.

[00

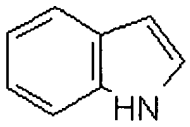
L3 ANSWER 9 OF 18 MEDLINE on STN DUPLICATE 7
AN 92133054 MEDLINE
DN 92133054 PubMed ID: 1776267
TI Decrease in albendazole sulphonation during experimental fascioliasis in sheep.
AU Galtier P; Alvinerie M; Plusquellec Y; Tufenkji A E; Houin G
CS Laboratoire de Pharmacologie-Toxicologie INRA, Toulouse, France.
SO XENOBIOTICA, (1991 Jul) 21 (7) 917-24.
Journal code: 1306665. ISSN: 0049-8254.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199203
ED Entered STN: 19920322
Last Updated on STN: 19920322
Entered Medline: 19920304
AB 1. The in vivo **S-oxidation** of albendazole was measured from the pharmacokinetic profile of albendazole sulphoxide and sulphone determined in young male sheep receiving oral albendazole (1.9 mg/kg). Studies were carried out before, and each month after, oral infestation by 150 metacercariae of Fasciola hepatica. 2. Parasitic pathology was ascertained by clinical observation of animals, and the increase in plasma antibodies directed against liver flukes. 3. Rate of conversion of sulphoxide to sulphone and rate of sulphone elimination, were respectively decreased by 47% and 87% at week 8 post-infection, whereas significant increases in the area under plasma sulphone concentrations versus time curve and mean residence time, occurred 4-12 weeks following the infestation. 4. A 58% decrease in albendazole sulphonation was demonstrated in liver microsomal preparations obtained from 8-week-infected sheep, while there was no change in the FAD-directed sulphoxidation of albendazole. 5. The transient impairment of albendazole sulphonation could be related to the decrease in liver microsomal **cytochrome P450**-dependent **monooxygenases** observed in sheep with a similar parasitic pathology.

L54 ANSWER 10 OF 11 MEDLINE on STN
AN 91042455 MEDLINE
DN 91042455 PubMed ID: 2233694
TI Stereoselective S-oxygenation of 2-aryl-1,3-dithiolanes by the flavin-containing and **cytochrome** P-450 **monooxygenases**.
AU Cashman J R; Olsen L D
CS Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, 94143-0446.
NC RRD16614 (NCRR)
SO MOLECULAR PHARMACOLOGY, (1990 Oct) 38 (4) 573-85.
Journal code: 0035623. ISSN: 0026-895X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199012
ED Entered STN: 19910208
Last Updated on STN: 19970203
Entered Medline: 19901204

AB The reaction of NaIO4, highly purified flavin-containing monooxygenase (EC 1.14.13.8), and microsomes from hog liver with 2-aryl-1,3-dithiolanes and 2-aryl-1,3-dithiolane S-oxides was investigated. The initial rates determined for the microsome- and purified flavin-containing monooxygenase-catalyzed rate of S-**oxidation** of para-substituted 2-aryl-1,3-dithiolanes were similar, demonstrating that S-**oxidation** of these **substrates** occurred with similar velocities at saturating concentrations of **substrate** and, at least for the first S-**oxidation**, the reaction was insensitive to the nature of the para-substituent. The diastereoselectivity of S-oxygenation of 2-aryl-1,3-dithiolanes was determined and, in general, a marked preference for addition of oxygen to the sulfide sulfur atom was observed to occur trans to the aryl groups. In all cases examined, enantioselective enzymatic S-**oxidation** was observed. For S-oxide formation in microsomes, the data provided evidence for a minor role of cytochrome P-450 in S-oxide formation, but the flavin-containing monooxygenase was mainly responsible for production of S-oxide. In contrast to previous reports, the enantioselectivity of S-**oxidation** catalyzed by highly purified cytochrome P-450IIB-1 and cytochrome P-450IIB-10 was not always opposite to that catalyzed by hog liver flavin-containing monooxygenase activity. 2-Aryl-1,3-dithiolane S-oxides were also oxidized a second time by NaIO4, microsomes, or highly purified flavin-containing monooxygenase from hog liver but not cytochrome P-450IIB-1 or P-450IIB-10. The rate of the second **oxidation** was 10-15-fold slower than the corresponding first S-**oxidation** and S,S'-dioxide formation was markedly dependent on the electronic nature of the para-substituent (Hammett correlation rho value of -1.3 and -1.1 for microsomes and highly purified flavin-containing monooxygenase from hog liver, respectively). The large dependence of the rate of S,S'-dioxide formation on the nature of the para-substituent demonstrates that velocity values at saturating concentrations of S-oxide were not the same for all 2-aryl-1,3-dithiolane S-oxides and suggests that the chemical nature of the 2-aryl-1,3-dithiolane S-oxide contributes to the rate-determining step of this enzymatic reaction.

[LinkDB]

ENTRY C00463
NAME Indole
2,3-Benzopyrrole
FORMULA C8H7N



C00463

REACTION R00673 R00674 R02338 R02339 R02340
PATHWAY PATH: MAP00380 Tryptophan metabolism
PATH: MAP00400 Phenylalanine, tyrosine and tryptophan biosynthesis
ENZYME 1.13.11.17 4.1.99.1
DBLINKS CAS: 120-72-9
///

Option:

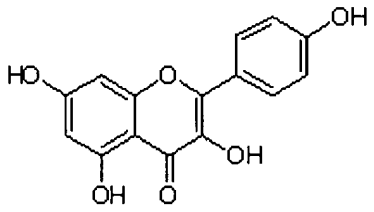
1. Launch ISIS/Draw ... See instructions for setup.

[KEGG | DBGET | GenomeNet]

h ge e bge b bge c

[LinkDB]

ENTRY C05903
NAME Kaempferol
3,4',5,7-tetrahydroxyflavone
4H-1-Benzopyran-4-one, 3,5,7-trihydroxy-2-(4-hydroxyphenyl)-
$5,7,4'-Trihydroxyflavonol
C.I. 75640
Flavone, 3,4',5,7-tetrahydroxy-
Indigo Yellow
Kaempherol
Kempferol
Nimbecetin
Pelargidenolon
Populnetin
Rhamnolutein
Rhamnolutin
Robigenin
Swartziol
Trifolitin
FORMULA C15H10O6



C05903

REACTION R03126 R05035
PATHWAY PATH: MAP00940 Flavonoids, stilbene and lignin biosynthesis
DBLINKS CAS: 520-18-3
///

Option:

1. Launch ISIS/Draw ... See instructions for setup.

[KEGG | DBGET | GenomeNet]

h ge e bge b bge c

L29 ANSWER 15 OF 25 MEDLINE on STN DUPLICATE 8
AN 97150876 MEDLINE
DN 97150876 PubMed ID: 8995412
TI An active site substitution, F87V, converts cytochrome **P450 BM-3** into a regio- and stereoselective (14S,15R)-arachidonic acid epoxygenase.
AU Graham-Lorence S; Truan G; Peterson J A; Falck J R; Wei S; Helvig C; Capdevila J H
CS Department of Biochemistry, University of Texas Southwestern Medical Center, Dallas 75235, USA.
NC GM 31278 (NIGMS)
GM 37922 (NIGMS)
GM 43479 (NIGMS)
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Jan 10) 272 (2) 1127-35.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199702
ED Entered STN: 19970227
Last Updated on STN: 19980206
Entered Medline: 19970212
AB Cytochrome **P450 BM-3** catalyzes the high turnover regio- and stereoselective metabolism of arachidonic and eicosapentaenoic acids. To map structural determinants of productive active site fatty acid binding, we mutated two amino acid residues, arginine 47 and phenylalanine 87, which flank the surface and heme ends of the enzyme's substrate access channel, respectively. Replacement of arginine 47 with glutamic acid resulted in a catalytically inactive mutant. Replacement of arginine 47 with alanine yielded a protein with reduced substrate binding affinity and arachidonate sp3 carbon hydroxylation activity (72% of control wild type). On the other hand, arachidonic and eicosapentaenoic acid epoxidation was significantly enhanced (154 and 137%, of control wild type, respectively). As with wild type, the alanine 47 mutant generated (18R)-hydroxyeicosatetraenoic, (14S,15R)-epoxyeicosatrienoic, and (17S,18R)-epoxyeicosatetraenoic acids nearly enantiomerically pure. Replacement of phenylalanine 87 with valine converted cytochrome **P450 BM-3** into a regio- and stereoselective arachidonic acid epoxygenase ((14S,15R)-epoxyeicosatrienoic acid, 99% of total products). Conversely, metabolism of eicosapentaenoic acid by the valine 87 mutant yielded a mixture of (14S,15R)- and (17S,18R)-epoxyeicosatetraenoic acids (26 and 69% of total, 94 and 96% optical purity, respectively). Finally, replacement of phenylalanine 87 with tyrosine yielded an inactive protein. We propose that: (a) fatty acid **oxidation** by **P450 BM-3** is incompatible with the presence of residues with negatively charged side chains at the surface opening of the substrate access channel or a polar aromatic side chain in the vicinity of the heme iron; (b) the high turnover regio- and stereoselective metabolism of arachidonic and eicosapentaenoic acids involves charge-dependent anchoring of the fatty acids at the mouth of the access channel by arginine 47, as well as steric gating of the heme-bound oxidant by phenylalanine 87; and (c) substrate binding coordinates, as opposed to oxygen chemistries, are the determining factors responsible for reaction rates, product chemistry, and, thus, catalytic outcome.

L29 ANSWER 17 OF 25 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1997:108967 BIOSIS
DN PREV199799408170
TI Oxygen activation by cytochrome **P450-BM-3**:
Effects of mutating an active site acidic residue.
AU Yeom, Hyeyeong; Sligar, Stephen G. (1)
CS (1) 405 N. Mathews Ave., Urbana, IL 61801 USA
SO Archives of Biochemistry and Biophysics, (1997) Vol. 337, No. 2, pp. 209-216.
ISSN: 0003-9861.
DT Article
LA English
AB A highly conserved acid residue is found in the I-helix of most cytochrome P450s and has been suggested to play a critical function in oxygen activation and substrate hydroxylation in these monooxygenases. We have investigated this hypothesis for cytochrome **P450-BM-3** by replacing the naturally occurring glutamate at position 267 with a glutamine residue. In the case of **P450-BM-3**, mutation of the glutamate to glutamine as position 267 drastically reduces the catalytic activity of the enzyme when palmitate is used as a substrate for hydroxylation. On the other hand, the activity change toward laurate hydroxylation is relatively small. The much slower catalytic turnover by the mutant enzyme in palmitate hydroxylation compared with wild type allows the observation of a new spectral intermediate in the hemoprotein. This intermediate is similar to that observed in the corresponding active site acid-to-amide replacement in cytochrome P450-cam (N. C. Gerber and S. G. Sligar (1994) J. Biol. Chem. 269, 4260-4266). Also, in analogy with P450-cam, this mutation does not lead to any side **oxidation** processes which produce hydrogen peroxide. Interestingly, however, the alteration in the active site structure which is implied by the change in regio specificity may also effect substrate packing thus leading to the uncoupling of the enzyme to produce additional water rather than a commitment to substrate **oxidation**. In addition, the distribution of hydroxylation products is altered by this mutation, suggesting some perturbation of the recognition property in **P450-BM-3**.

L29 ANSWER 20 OF 25 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
AN 1995:156090 BIOSIS
DN PREV199598170390
TI Structure and function of cytochromes P450: A comparative analysis of three crystal structures.
AU Hasemann, Charles A.; Kurumbail, Ravi G.; Boddupalli, Sekhar S.; Peterson, Julian A.; Deisenhofer, Johann (1)
CS (1) Dep. Biochem., Univ. Texas Southwestern Med. Cent., 5323 Harry Hines Blvd., Dallas, TX 75235-9050 USA
SO Structure (London), (1995) Vol. 3, No. 1, pp. 41-62.
ISSN: 0969-2126.
DT Article
LA English
AB Background: Cytochromes P450 catalyze the **oxidation** of a variety of hydrophobic substrates. Sequence identities between P450 families are generally low (10-30%), and consequently, the structure-function correlations among P450s are not clear. The crystal structures of P450-terp and the hemoprotein domain of P450-BM-3 were recently determined, and are compared here with the previously available structure of P450-cam. Results: The topology of all three enzymes is quite similar. The heme-binding core structure is well conserved, except for local differences in the I helices. The greatest variation is observed in the substrate-binding regions. The structural super-position of the proteins permits an improved sequence alignment of other P450s. The charge distribution in the three structures is similarly asymmetric and defines a molecular dipole. Conclusions: Based on this comparison we believe that all P450s will be found to possess the same tertiary structure. The ability to precisely predict other P450 substrate-contact residues is limited by the extreme structural heterogeneity in the substrate-recognition regions. The central I-helix structures of P450-terp and **P450-BM-3** suggest a role for helix-associated solvent molecules as a source of catalytic protons, distinct from the mechanism for P450-cam. We suggest that the P450 molecular dipole might aid in both redox-partner docking and proton recruitment for catalysis.